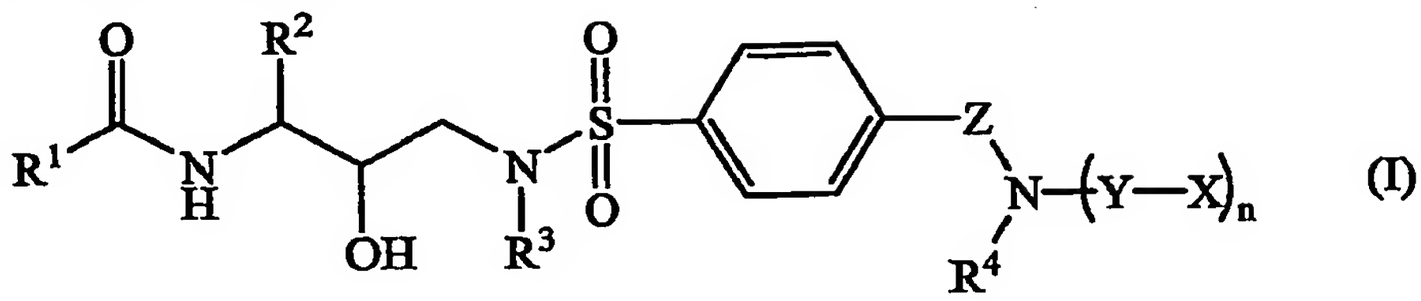
CLAIMS

1. A prodrug having the formula



(I)

the stereoisomeric form or salt thereof, wherein

n is 1, 2, 3, 4 or 5;

Y is proline, alanine, hydroxyproline, dihydroxyproline, thiazolidinecarboxylic acid (thioproline), dehydroproline, pipecolic acid (L-homoproline), azetidinecarboxylic acid, aziridinecarboxylic acid, glycine, serine, valine, leucine, isoleucine and threonine;

X is selected from any amino acid in the D- or L-configuration;

X and Y in each repeat of [Y-X] are chosen independently from one another and independently from other repeats;

Z is a direct bond or a bivalent straight or branched saturated hydrocarbon group having from 1 to 4 carbon atoms;

R^1 is an aryl, heteroaryl, aryloxy, heteroaryloxy, aryloxyC_{1-4}alkyl, heterocycloalkyloxy, heterocycloalkylC_{1-4}alkyloxy, heteroaryloxyC_{1-4}alkyl, heteroarylC_{1-4}alkyloxy;

R^2 is arylC_{1-4}alkyl;

R^3 is C_{1-10}alkyl, C_{2-6}alkenyl or C_{3-7}cycloalkylC_{1-4}alkyl;

R^4 is hydrogen or C_{1-4}alkyl;

aryl, when used alone or in combination with another group, means phenyl optionally substituted with one or more substituents each individually selected from the group consisting of C_{1-4}alkyl, hydroxy, C_{1-4}alkyloxy, nitro, cyano, halo, amino, mono- or di(C_{1-4}alkyl)amino and amido;

heteroaryl, when used alone or in combination with another group, means a monocyclic or bicyclic aromatic heterocycle having one or more oxygen, sulphur or nitrogen heteroatoms, which aromatic heterocycle may optionally be substituted on one or more carbon atoms with a substituent selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, amino, hydroxy, aryl, amido, mono- or di(C_{1-4}alkyl)amino, halo, nitro, heterocycloalkyl and C_{1-4}alkyloxycarbonyl, and which aromatic heterocycle may also be optionally substituted on a secondary nitrogen atom by C_{1-4}alkyl or arylC_{1-4}alkyl;

heterocycloalkyl, when used alone or in combination with another group, means a saturated or partially unsaturated monocyclic or bicyclic heterocycle having one or more oxygen, sulphur or nitrogen heteroatoms, which heterocycle may optionally be substituted on one or more carbon atoms with a substituent selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkyloxy, hydroxy, halo and oxo, and which heterocycle may also be optionally substituted on a secondary nitrogen atom by C_{1-4}alkyl or arylC_{1-4}alkyl.

2. A prodrug as claimed in claim 1 wherein each X independently is selected from a naturally occurring amino acid.

3. A prodrug as claimed in claim 1 or 2 wherein n is 1, 2 or 3.

4. A prodrug as claimed in any one of claims 1 to 3 wherein n is 2 or 3 and wherein at least one X is an hydrophobic or aromatic amino acid.

5. A prodrug as claimed in any one of claims 1 to 4 wherein n is 2 or 3 and wherein at least one X is an neutral or acidic amino acid.

6. A prodrug as claimed in any one of claims 1 to 5 wherein n is 2 or 3 and wherein at least one X is a basic amino acid.

7. A prodrug as claimed in any one of claims 1 to 6 wherein $-(Y-X)_n$ comprises amino-terminally X-Pro, X-Ala, X-Gly, X-Ser, X-Val, or X-Leu.

8. A prodrug as claimed in any one of claims 1 to 7 wherein $-(Y-X)_n$ comprises amino-terminally X-proline or X-alanine.

9. A prodrug as claimed in any one of claims 1 to 8 wherein each Y independently is proline, alanine, glycine, serine, valine or leucine.

10. A prodrug as claimed in any one of claims 1 to 9 wherein each Y independently is proline or hydroxyproline or dihydroxyproline or alanine.

11. A prodrug as claimed in any one of claims 1 to 10 wherein each Y independently is proline or alanine.

12. A prodrug as claimed in any one of claims 1 to 11 wherein $-(Y-X)_n$ is $-(Y-X)_{1or2}$-Y-Val.

13. A prodrug as claimed in any one of claims 1 to 12 wherein $-(Y-X)_n$ is $-(Y-X)_{1or2}$-Pro-Val.

14. A prodrug as claimed in any one of claims 1 to 13 wherein the $(Y-X)_n$ oligopeptide is built up with (Y-X) repeats selected from the group consisting of Pro-Val,

Pro-Asp, Pro-Ser, Pro-Lys, Pro-Arg, Pro-His, Pro-Phe, Pro-Ile, Pro-Leu, Ala-Val, Ala-Asp, Ala-Ser, Ala-Lys, Ala-Arg, Ala-His, Ala-Phe, Ala-Ile and Ala-Leu.

15. A prodrug as claimed in any one of claims 1 to 14 wherein R^1 is heterocycloalkyloxy, heteroaryl, heteroarylC_{1-4}alkyloxy, aryl or aryloxyC_{1-4}alkyl.

16. A prodrug as claimed in any one of claims 1 to 15 wherein R^1 is hexahydrofuro[2,3-b]furan-3-yl-oxy, tetrahydrofuran-3-yl-oxy, quinolin-2-yl, thiazol-5-ylmethyloxy, 3-hydroxy-2-methyl-1-phenyl, 2,6-dimethylphenoxymethyl.

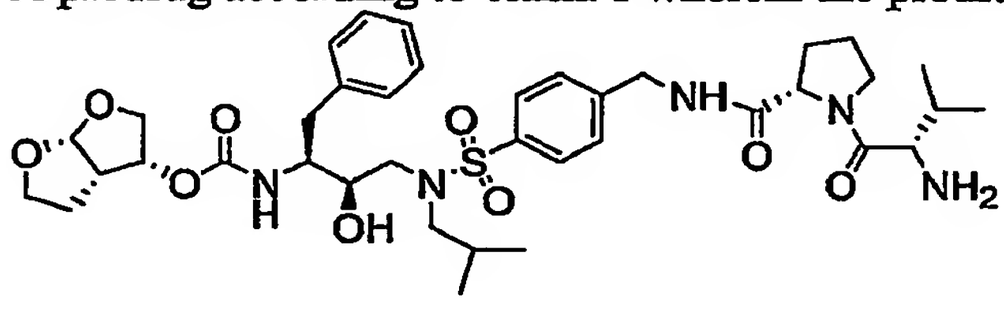
17. A prodrug as claimed in any one of claims 1 to 16 wherein R^1 is hexahydrofuro[2,3-b]furan-3-yl-oxy, tetrahydrofuran-3-yl-oxy, quinolin-2-yl, thiazol-5-ylmethyloxy, 3-hydroxy-2-methyl-1-phenyl, 2,6-dimethylphenoxymethyl.

18. A prodrug as claimed in any one of claims 1 to 17 wherein R^1 is (3R, 3aS, 6aR)-hexahydrofuro[2,3-b]furan-3-yl-oxy.

19. A prodrug as claimed in any one of claims 1 to 18 wherein R^2 is phenylmethyl; R^3 is isobutyl and R^4 is hydrogen.

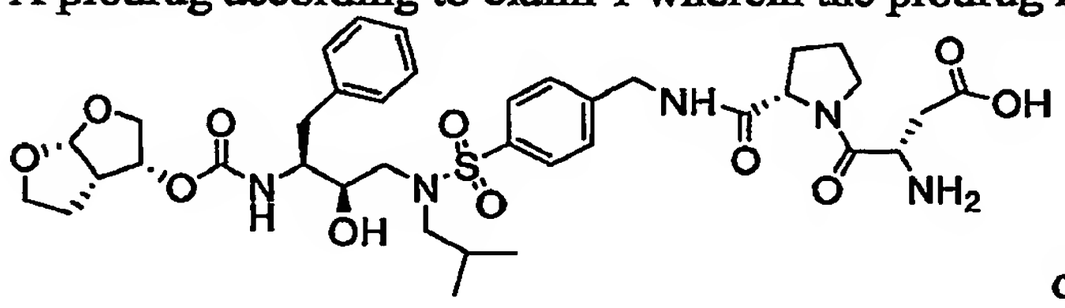
20. A prodrug as claimed in any one of claims 1 to 19 wherein Z is methylene.

21. A prodrug according to claim 1 wherein the prodrug is



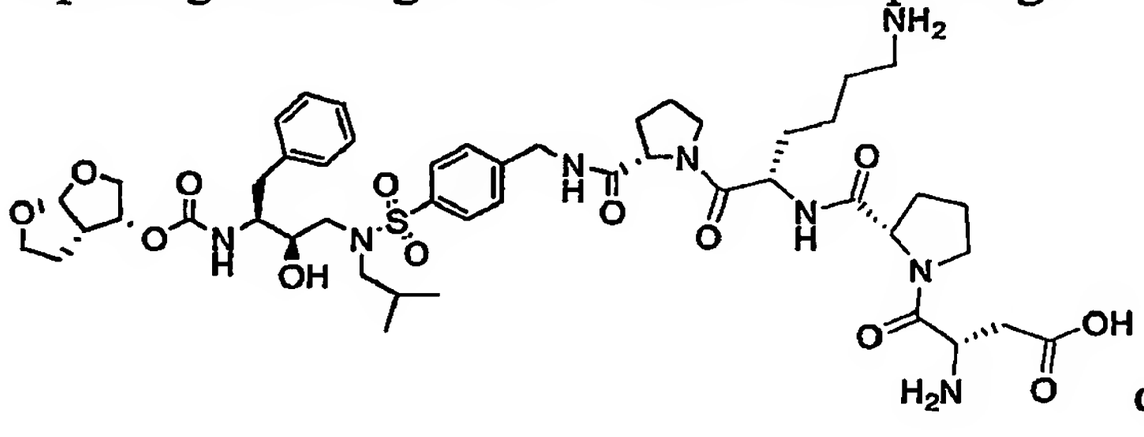
or a salt thereof.

22. A prodrug according to claim 1 wherein the prodrug is



or a salt thereof.

23. A prodrug according to claim 1 wherein the prodrug is



or a salt thereof.

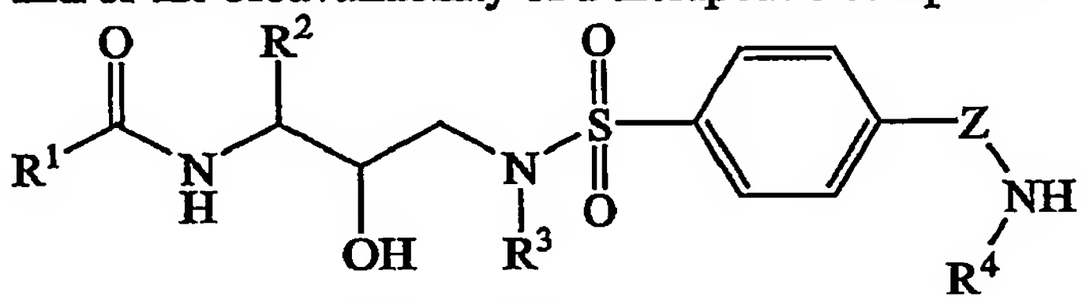
24. A prodrug according to any one of claims 1 to 23 for use as a medicine.

25. Use of a prodrug according to any one of claims 1 to 23 for the manufacture of a medicament useful for preventing or treating HIV infection.

26. A method of preventing or treating HIV infection by administering to any host, including a human, a non-human animal and mammals, a prodrug according to any one of claims 1 to 23 in an amount effective to prevent or treat the HIV infection.

27. A pharmaceutical preparation which contains an effective dose of at least one of the prodrugs as claimed in any one of claims 1 to 23 in addition to customary pharmaceutically innocuous excipients and auxiliaries.

28. A method for modulating the water solubility, modulating plasma protein binding and/or the bioavailability of a therapeutic compound

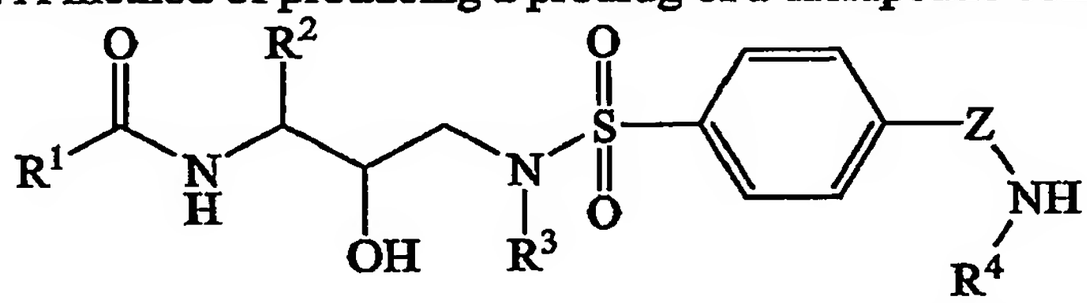


(Ia)

by coupling a peptide of formula H-(X-Y)$_n$ to said prodrug wherein n, X, Y, R^1, R^2, R^3, R^4 and Z are as defined in any one of claims 1 to 23 and wherein the resulting conjugate is cleavable by a dipeptidyl-peptidase.

29. A method according to claim 28 wherein the dipeptidyl-peptidase is CD26.

30. A method of producing a prodrug of a therapeutic compound



(Ia)

wherein the prodrug is cleavable by a dipeptidyl-peptidase, the method comprising the step of linking a therapeutic compound and a peptide of formula H-(X-Y)$_n$ wherein n, X, Y, R^1, R^2, R^3, R^4 and Z are as defined in any one of claims 1 to 20 and wherein the resulting conjugate is cleavable by a dipeptidyl-peptidase.

31. A method according to claim 30 wherein the dipeptidyl-peptidase is CD26.